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Tamoxifen-Induced Lupus Erythematosus

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Abstract

Introduction: Anti Nuclear Antibodies are one of the auto antibodies which are involved in screening, diagnosis and pathology of some auto and non autoimmune and drug induced diseases including Lupus Erythrymatosus.

Objectives: The aim of this study is to investigate, if there is any correlation between tamoxifen side effects and the blood levels of Anti Nuclear Antibodies as a consequence of drug-induced lupus erythematosus.

Methods: Twenty-eight breast cancer patients under tamoxifen therapy were involved in this study and compared to 11 newly diagnosed breast cancer patients who did not receive any therapy. 5 mls of intravenous blood were collected from the subjects after informed consent was obtained. The plasma was separated and the ANA levels were determined using ELISA.

Results: Seventeen patients under tamoxifen were found with high level of ANA while 11 patients were with normal levels of ANA. However, the mean ANA plasma level in patients under tamoxifen therapy was 155.39 U/ml (9.4-911.7 U/ml) compared to 11.31 U/ml (0.9-29 U/ml) in the newly diagnosed patients; the ANA level significantly increased (p value was 0.017). The patients under tamoxifen therapy were divided to five groups according to the number of tamoxifen therapies they received. Group 1 of 4 patients: received one tamoxifen therapy, group 2 of 6 patients: received three therapies, group 3 of 5 patients: received 5 therapies, group 4 of 9 patients: received 6 therapies and group 5 of 4 patients: received therapies ≥ 10. When the means of ANA concentration were compared to the mean of the newly diagnosed patients the p values were 0.88, 0.26, 0.09, 0.04 and 0.17 respectively.

Conclusions: This study concluded that, although tamoxifen therapy did not affect the ANA level in all the patients, it significantly increased the blood level of ANA.

Keywords: Hormonal therapy; ANA; Breast cancer; Sudanese subjects; Tamoxifen

Introduction

Tamoxifen is an antagonist of estrogen receptor in breast tissues and it is agonist of estrogen receptor in endometrium [1]. It has been the standard endocrine (anti-estrogen) therapy for hormone receptor-positive breast cancer in pre and postmenopausal women, although aromatase inhibitors have been proposed. Tamoxifen and its metabolites bind the estrogen receptor and inhibit the binding of estrogen leading to inhibition of cell growth. Some studies showed that Tamoxifen has anti angiogenesis activity besides blocking of the estrogen receptor [2].

It is known that Tamoxifen has a number of side effects including its effect on inhibiting osteoclasts leading to prevention of osteoporosis [3], increasing the risk of endometrial cancer [4], increasing blood level of triacylglycerols and its medical complications and increasing the risk of fatty liver [5].

Drug-induced lupus erythematosus is an autoimmune disorder that is brought on by a reaction to medication. It is caused by a hypersensitivity reaction to a medication. The drug may react with cell materials, causing the body to form antibodies that attack the body's own healthy cells. The autoantibodies are known as Anti Nuclear Antibodies (ANA). Persons with drug-induced lupus erythematosus may have symptoms that affect the joints (arthritis), heart, lungs, kidney and nervous system [6].

Antinuclear antibodies (ANAs) are a specific class of autoantibodies that are secreted in response to destroyed or dead cells, with two subtypes; Autoantibodies against DNA and histones and Autoantibodies to extractable nuclear antigens. ANA were discovered and found to be associated with diagnosis of different diseases including connective tissue diseases [7]. The ANA test is frequently used as one criterion for the screening and diagnosis of lupus erythematosus (LE) [8]. However, high blood levels of ANA were found among breast cancer patients [9].

The objective of this study is to investigate, if there is any correlation between tamoxifen side effects and the blood levels of Anti Nuclear Antibodies as a consequence of drug-induced lupus erythematosus.

Patients, Material and Methods

Study population

28 Sudanese patients with breast cancer under tamoxifen therapies suffering from fever, joint pain and loss of appetite (symptoms of drug-induced lupus erythematosus) were involved in this study and compared to eleven newly diagnosed breast cancer patients who did not receive any breast cancer treatment and without the mentioned symptoms. The range of age of patients under treatment was (30-84) and the mean was 52.3 while the age range of the control subjects was (30-73) and their mean was 51.

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Ethical clearance

An ethical license was obtained from the faculty of Science University of Khartoum and approved from the Ministry of Health. The study subjects were involved in this study after informed consent.

Research design

According to research method, this study can be classified as non experimental, quantitative, descriptive, case control and hospital based study.

Sampling

5 mls of intravenous blood samples were obtained from each study subject and the serum was separated and stored at -20°C.

Methods

ELISA kit from human diagnostics company (ITC70001) was used to determine the ANA units as follows: Samples were allowed to reach room temperature (in 30 min), then diluted to 1:100 dilution, 100 µl of the diluted samples, Standards or calibrators (0, 31.25, 62.5, 125, 250, 500 U/ml), Positive and Negative Control Serum and blank (Phosphate buffer, pH 7.2 ± 0.2) were pipette into Micro titer ELISA plates coated with hela cell nuclei, ELISA plate was sealed with adhesive strip, and incubated for 1 hour at the room temperature. Then the solution was discarded from the ELISA plate which was washed 3 times with 300 µl Washing Buffer (TRIS buffer, pH 6.9 ± 0.2) per well, then 100 µl antihuman IgG bound to Horse Radish Peroxidase (HRP) was Pipette and Incubated for 30 min at room temperature. The solution was removed from the ELISA plate and another wash was done as previously described. 100 µl of substrate (hydrogen peroxide) and Tetra Methyl Benezidine chromogen (TMB), pH 3.7 ± 0.2, was pipetted and incubated for 10 minutes at room temperatures, then 100 µl stop solution (Sulphuric acid, 0.5 mol/l) was added to each well. After that the absorbance values was read at 450 nm and the concentration of each sample determined.

Statistical Package for Social Sciences (SPSS) software was used to analyze the obtained results. Data were reported as means ± standard deviation, statistical analysis was performed by t-test analysis for variance. For all statistical tests a p value less than 0.05 was taken to indicate statistical significance.

Results

The analysis showed that all the newly diagnosed patients (control group) had negative ANA values according to manufacturer (less than 40 U/ml), however, from the 28 tamoxifen treated patients (exposed group) 17 patients were with high ANA levels compared to the control group. The ranges, mean, Standard Deviation and p value of ANA results of the control and exposed subjects are shown in table 1. The mean values of ANA in the control and exposed groups are compared in figure 1.

The patients under tamoxifen therapy were divided to five groups according to the number of tamoxifen therapies they received. Group 1 of 4 patients: received one tamoxifen therapy and the mean ANA level was 12.02 U/ml, group 2 involved 6 patients: received three therapies with 152.07 U/ml mean ANA, group 3 with 5 patients: received 5 therapies; their mean value of ANA level was 72.24 U/ml, group 4 of 9 patients: received 6 therapies and their mean ANA value was 259.44 U/ml and group 5 of 4 patients: received more than 10 therapies with 173.52 U/ml mean ANA level (Figure 2). When the means of ANA concentration of the different groups were compared to the mean of the newly diagnosed patients (11.31 U/ml) the p values were 0.88, 0.26, 0.09, 0.04 and 0.17 respectively. From the above results it is clear that the ANA blood level increases with increase of doses.

Discussion

All the newly diagnosed patients were with negative ANA results; this finding is similar to the finding of Derk [10] who registered negative ANA testing in breast cancer patients. In contrast Imran et al.

	Range (U/ml)	Mean (U/ml)	STD	P- value
Tamoxifen treated patients	9.4-911.7	155.39	234.74	0.017
Newly diagnosed patients	0.9-29	11.31	8.74	

Table 1: ANA results in the control and exposed groups.

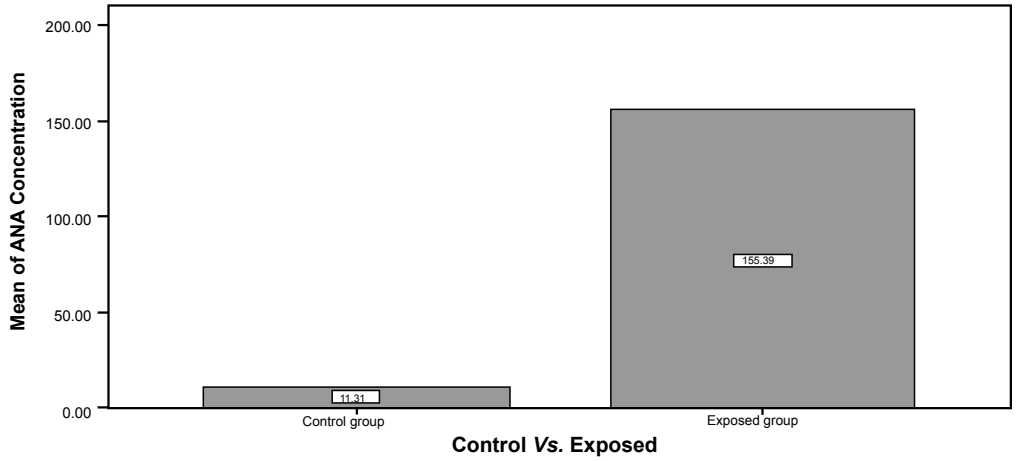

Figure 1 clearly showed that the mean values of ANA of the exposed group (breast cancer patients under tamoxifen therapy) are very high than the mean values of the control group (newly diagnosed breast cancer patients who did start any treatment).

Figure 1: Mean values of ANA in Tamoxifen treated (exposed) and control subjects.

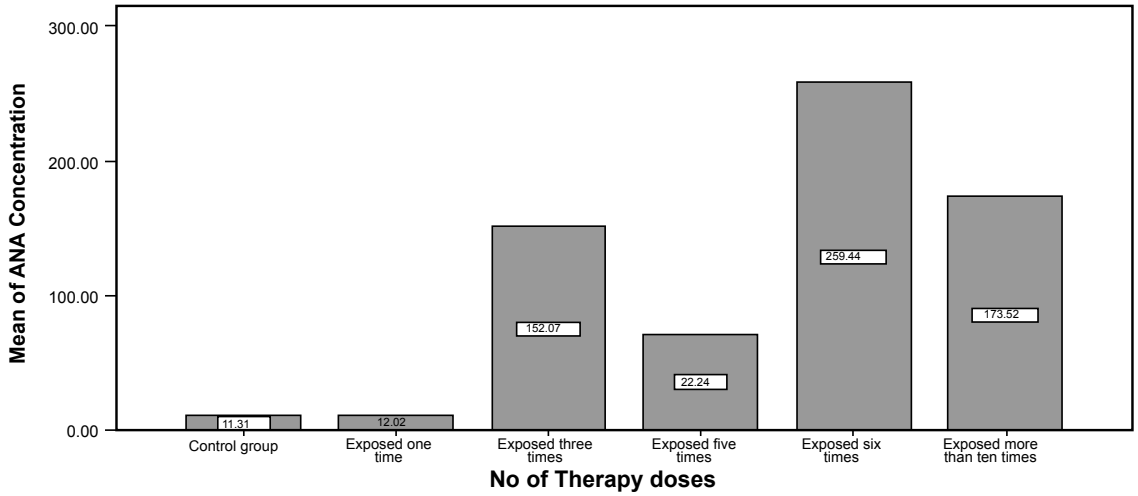

Figure 2 reflected that the mean value of ANA in the different exposed groups was fluctuating and it has no systemic behavior and this probably due to the small number of patients in each group. However, the general pattern is that, the ANA level increases with the increase of the number of therapies.

Figure 2: Mean values of ANA levels among the five groups of tamoxifen treated (exposed) patients and the control group.

[11] and Tschernatsch and his colleagues [12] found that positive ANA tests was frequently seen in patients with breast cancer.

Compared to the newly diagnosed breast cancer patients, seventeen patients under tamoxifen were found with high level of ANA while 11 patients were with normal levels of ANA. This, strongly push towards personalized medicine. However, when the means were compared it was clear that the difference between the mean of ANA values in patients under tamoxifen therapy (155.39 U/ml) and in the newly diagnosed patients (11.3 U/ml) was significant (p=0.017). In contrast to our findings Imai research group [13] concluded that chemotherapy of hepatocellular carcinoma decreased the blood level of ANA. Similar to our results, the study of Slater and his colleagues [14] revealed that ANA positive is more frequently associated with receiving chemotherapy. Increased ANA level may be the cause of lupus erythematosus symptoms in the patients of breast cancer under tamoxifen therapy. However, similar to our findings Abu-Shakra scientific team [15] registered presence of rheumatoid symptoms and increased blood ANA level in breast cancer patients who received combinations of chemotherapy. However, this increase in ANA level may be due to the increased cell death because of the breast cancer therapy which in turn stimulates the immune system to produce the ANA against the constituents of theses dead cells.

Conclusions

1. Newly diagnosed breast cancers are associated with negative ANA testing.
2. Tamoxifen therapy is mostly accompanied by symptoms of lupus erythematosus as side effects.

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